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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/466,935	12/20/1999	VITALIY ARKADYEVICH LIVSHITS	0010-1070-0	1750

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AJINOMOTO CORPORATE SERVICES, LLC
INTELLECTUAL PROPERTY DEPARTMENT
1120 CONNECTICUT AVE., N.W.
WASHINGTON, DC 20036

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17 and 37-63* is/are pending in the application.

4a) Of the above claim(s) *49-63* is/are withdrawn from consideration.

5)☒ Claim(s) *16* is/are allowed.

6)☒ Claim(s) *17 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 16-17 and 37-63 are pending in the application.

[2] Applicants' filing of a reply under 37 CFR 1.111, filed September 07, 2004, to the Office action mailed May 04, 2004, is acknowledged.

[3] Applicants' amendment to the claims, filed September 07, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Claims 49-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[5] Claims 16-17 and 37-48 are being examined on the merits.

[6] Applicants are reminded to submit amended claims according to the revised amendment practice under 35 U.S.C. 1.121. It is noted that the status identifier "previously canceled" as used as a status identifier of claims 18-36 is improper. Claims 18-36 should be identified as "canceled."

[7] Applicants' arguments filed on September 07, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claims Rejections – 35 USC 112, Second Paragraph

[9] The rejection Claims 17 and 37-48 as being indefinite in the recitation of "an activity of a protein which imparts L-threonine resistance" or "an activity of a protein which imparts L-homoserine resistance" is maintained for the reasons of record as set forth at item [4] part [a] of the Office action mailed May 04, 2004.

[10] RESPONSE TO ARGUMENT: Applicants argue the terms "L-threonine resistance" and "L-homoserine resistance" are defined at pp. 6-8 of the specification, particularly at p. 7. Applicants' argument is not found persuasive.

While it is acknowledged that the specification defines the terms "L-threonine resistance" and "L-homoserine resistance" at pp. 6-8, it is noted that the definition of "L-threonine resistance" as defined in the specification is in conflict with that provided by applicants. The specification states that the concentration of L-threonine at which a wild-type will not grow is >30 mg/mL (p. 7), while applicants state this concentration is 39 mg/mL. Applicants are requested to clarify this inconsistency. Moreover, it is noted that, while the terms "L-threonine resistance" and "L-homoserine resistance" are defined in the specification, the specification fails to define the "activity" of a protein that imparts "L-threonine resistance" or "L-homoserine resistance" such that one of skill in the art could increase such an activity. It is suggested that applicants clarify the intended activity or activities that has/have the effect(s) of imparting "L-threonine resistance" or "L-homoserine resistance" in a bacterium comprising the protein.

[11] The rejection of claims 39, 42, 45, and 48 as being unclear in the recitation of "functions efficiently" is maintained for the reasons of record as set forth at item [4] part [a] of the Office action mailed May 04, 2004.

[12] RESPONSE TO ARGUMENT: Applicants argue the plain meaning of the words indicates that the term is meant to indicate a promoter that causes DNA to express protein in an amount higher than another promoter in an efficient manner and that the new promoter "functions efficiently" if the protein expression is higher than with the original promoter. Applicants' argument is not found persuasive.

It remains unclear as to applicants' intended meaning of the term "functions efficiently." Applicants' attempted clarification of the term by asserting that a promoter that increases gene expression in an "efficient manner" is a promoter that "functions efficiently" is not sufficient. It remains unclear as to how efficient a promoter must function to be included within the scope of those promoters that "function efficiently" and those that do not. As such, it is unclear as to the scope of promoters that applicants intend to be those that function efficiently and those that do not. It is suggested that applicants clarify the meaning of the term.

Claims Rejections – 35 USC 112, First Paragraph

[13] In view of the amendment to the claims, the written description rejection of claim 17 under 35 U.S.C. 112, first paragraph, as set forth at item [5] of the Office action mailed May 04, 2004 is withdrawn. Applicants have amended the claim such that it is clear as to the protein's activity, *i.e.,* imparting L-threonine resistance to a bacterium.

[14] The written description rejection of claims 37-48 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [5] of the Office action mailed May 04, 2004 and for the reasons stated below.

[15] RESPONSE TO ARGUMENT: Addressing means to increase DNA expression, applicants argue the specification exemplifies two such means – copy number amplification by introduction of a multi-copy vector, phage, or transposon comprising the nucleic acid into a bacterium, and promoter substitution. Applicants argue the crux of the invention is overexpression of SEQ ID NO:1 and 3 results in increased L-amino acid production and is not how to increase DNA expression, which applicants allege, is a known procedure that is well-known and thus need not be described. Addressing the use of any promoter sequence, applicants argue the skilled artisan can go to the prior art to determine other promoter sequences that would increase "efficiency" of expression. Applicants provide two prior art references, Cunning et al. and Walker et al., as support for the use of alternative promoters and the use of promoter substitution. Applicants argue that, based on the cited references, such methods were known in the art at the time of the invention. Applicants' argument is not found persuasive.

In this case, the genus of modified bacteria of claims 37-48 encompasses species that are not so limited to those that are modified by copy number amplification by introduction of a multi-copy vector, phage, or transposon comprising the nucleic acid into a bacterium, and promoter substitution using art-recognized promoters. The specification discloses only two representative species of the genus of claimed modified *E. coli* bacteria, *i.e.,* a bacterial host cell comprising an expression vector, wherein the

expression vector has a nucleic acid encoding the polypeptide of SEQ ID NO:2 or 4. These two representative species fail to represent the genus of claimed modified *E. coli* bacteria, which, as stated in a previous Office action and undisputed by applicants, is a widely variant genus, the broadest claims encompassing bacteria having any modification that achieves increased "activity." In addition to the two representative species as disclosed in the specification, the genus of modified *E. coli* bacteria encompass widely variant species, including (but not limited to) those having modification(s) of the endogenous promoter and/or enhancer elements and altered expression of proteins that regulate transcription and/or translation. While applicants attempt to dismiss the modification of the claimed genus of *E. coli* bacteria, asserting that this is not the crux of the invention, it is noted that the bacterial modification to "increase an activity of a protein" is an essential or critical feature of the claimed invention. The specification should describe such essential or critical features. In this case the specification does not. Regarding the genus of promoters that function "efficiently" in a bacterium, as stated above, it remains unclear as to the scope of promoters that applicants intend as those that function "efficiently." If one of skill is unclear as to the scope of intended promoters, it is unclear as to how one is to know whether one is in possession of the genus of recited promoters. As such, one of skill would recognize that applicants were not in possession of the claimed invention. Even assuming *arguendo* one of skill were to recognize the intended scope of promoters that function "efficiently," it is noted that the specification fails to disclose the sequence of the promoter of the "gene coding for the protein" such that one could replace the promoter

of the "gene coding for the protein" with another. Even if the promoter sequence is within the nucleotide sequence of SEQ ID NO:1, there is no indication as to which of those nucleotides are the promoter sequence such that one could replace those nucleotides with another promoter of the prior art.

[16] The scope of enablement rejection of claims 17 and 37-48 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [6] of the Office action mailed May 04, 2004 and for the reasons stated below.

[17] RESPONSE TO ARGUMENT: Addressing the enablement of the modified bacteria of claims 37-48, applicants argue methods of increasing gene expression are known in the art and the disclosure in combination with the prior art enables the full scope of the claimed invention. Applicants' argument is not found persuasive.

As stated above, the scope of modified bacteria of claims 37-48 broadly encompasses modified bacteria that are not limited to those that are modified by copy number amplification by introduction of a multi-copy vector, phage, or transposon comprising the nucleic acid into a bacterium, and promoter substitution using art-recognized promoters. In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of experimentation required to make the full scope of the claims (see the detailed analysis of the Factors of *In re Wands* as set forth at pages 9-12 of the Office action mailed May 04, 2004), the specification in combination with the prior art fails to enable the full scope of the claims.

Addressing the enablement of the DNAs of claims 17 and 43, applicants state that "it is unclear what the bases are for such a rejection." Applicants assume the rejection is based on the high level of unpredictability in making alterations to an protein-encoding DNA sequence. Applicants provide a FASTA sequence search of SEQ ID NO:3, allegedly demonstrating the highly conserved nature of SEQ ID NO:3 among gram-positive bacteria, such that a skilled artisan could determine amino acid positions that are amenable to alteration. Applicants argue that a skilled artisan would change those residues that are non-conserved, those being residues that are not likely necessary for function. Applicants' argument is not found persuasive.

Applicants' assumption is correct in part. As stated in the previous Office action, the rejection of claims 17 and 43 as directed to the scope of DNAs of parts (b) is based on the Factors of *In re Wands* including the breadth of the claims, the guidance and working examples in the specification, the high level of unpredictability as evidenced by the state of the art, and the amount of experimentation required to make the full scope of DNAs of claim 17 and bacteria of claim 43. Applicants' attention is directed to pages 9-12 of the Office action mailed May 04, 2004. The examiner acknowledges applicants' evidence, however, it is unclear as to whether the protein sequences shown in the alignment were available to one of skill in the art and appropriately annotated to describe their function at the time of the invention. Applicants are reminded that the specification should be enabling at the time of the invention. If the amino acid sequences were not available and/or not properly annotated to describe their function at the time of the invention, one could not (if not available) or would not (if not annotated

as threonine resistance proteins) include such sequences in an alignment for the determination of conserved/non-conserved amino acids for imparting threonine resistance. Moreover, even assuming all sequences were available and properly annotated at the time of the invention, it is noted that some of the protein sequences listed in applicants' FASTA search appear to be annotated as proteins that are not involved in threonine resistance or their function has not been confirmed as imparting threonine resistance, *e.g.,* those protein sequences that are annotated as having unknown function, putative function, or function other than imparting threonine resistance. Thus, at least for those proteins that are not annotated as being proteins known to be involved in threonine resistance, one of skill would not include such sequences in an alignment for the determination of amino acids that are conserved/non-conserved for imparting threonine resistance.

Conclusion

[18] Status of the claims:

- Claims 16-17 and 37-63 are pending in the application.
- Claims 49-63 are withdrawn from consideration.
- Claims 17 and 37-48 are rejected.
- Claim 16 is in condition for allowance.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652
10-13-04